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Importance of Lymph Node Metastases in Primary Peritoneal Carcinoma

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Background and Objectives: The incidence and significance of lymph node involvement in patients with primary peritoneal adenocarcinoma (PPA) are unknown. The aim of the current study is to report on the incidence and significance of clinically or surgically detectable lymphadenopathy in women with PPA.
Methods: The study is a retrospective clinical review of patients with the confirmed diagnosis of PPA treated at Roswell Park Cancer Institute between 1982 and 1996. Patients with clinically or surgically detectable lymphadenopathy confirmed on histologic examination to be secondary to metastases from PPA were identified and compared to patients with negative lymph nodes with regard to clinicopathologic characteristics, treatment, response to treatment, and survival.
Results: Seventy-two patients with PPA were identified. Pelvic and periaortic lymph node biopsies or sampling were performed in 35% of the patients. In 8/72 patients (11%), lymphadenopathy was one of the presenting clinical or surgical findings. The clinicopathologic features, treatment, response to first-line chemotherapy, and estimated median overall survival were not different in patients with or without lymph node involvement (71.4% vs. 69.7%, $P = 1.0$, and 21.5 vs. 23.5 months, $P = 0.14$).
Conclusions: Lymph node involvement is not an infrequent occurrence in patients with PPA and does not seem to be of adverse prognostic significance. *J. Surg. Oncol. 1998;68:144–148.*

KEY WORDS: primary peritoneal adenocarcinoma; lymph nodes; survival

INTRODUCTION

Primary peritoneal adenocarcinoma (PPA) is a disease frequently encountered by surgeons and gynecologists. PPA was first recognized as a separate disease entity by Swerdlow [1] in 1959 and is basically characterized by widely spread intraperitoneal carcinomatosis and normal-sized ovaries. Although the clinicopathologic features of PPA have been described in several reports [2–17], the clinical behavior of this disease and its pathologic spread patterns remain obscure. PPA is thought to constitute 13.8% of patients with serous [14] or epithelial [15] ovarian cancer. Although it seems likely that PPA spreads by surface implantation, reports of lymph node and parenchymal liver metastases [12,14] indicate that lymphatic or hematogenous dissemination may be possible.

There is no distinct staging system for PPA. The International Federation of Gynecology and Obstetrics (FIGO) staging system for patients with ovarian cancer [18], which has been traditionally employed for patients with PPA, stratifies patients with positive pelvic, peri-

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aortic, or inguinal lymph nodes to stage III, and patients with positive supraclavicular or axillary lymph nodes to stage IV. Though lymphatic spread of epithelial ovarian carcinoma has been the focus of several reports [19–21] in the last 2 decades, very little is known about the lymphatic spread potential of PPA. The aim of the present report is to describe the incidence and significance of lymphadenopathy as one of the clinical or surgical presenting features in women with PPA.

MATERIALS AND METHODS

A computerized search of all female patients coded or cross-coded as peritoneal adenocarcinoma by the tumor registry of Roswell Park Cancer Institute (RPCI) was performed. The operative and pathological reports and medical records of these patients were reviewed. Pathological slides were reviewed by one of the coauthors (B.A.W.). The diagnosis of PPA was based on the following criteria: (1) the ovaries were either absent or normal in size (<4.0 cm largest diameter); (2) the involvement in the extraovarian sites was greater than the involvement on the surface of either ovary; (3) microscopically, the ovaries were either not involved with tumor or exhibited only serosal or cortical implants less than 5 × 5 mm in size [17]; and (4) the histological and cytological characteristics of the tumor were predominantly of the serous type. None of the patients had evidence of other primary cancers that might explain the peritoneal involvement. Patients with peritoneal mesothelioma, borderline peritoneal tumors, and invasive ovarian cancer (more than 5 × 5 mm ovarian involvement) were excluded from the study population.

Surgical staging was performed according to the FIGO staging criteria for ovarian cancer [18] based on the operative and pathological data available for each patient. Our protocol for management of patients with PPA does not employ routine systematic pelvic and/or periaortic lymphadenectomy. The pelvic and periaortic lymph nodes are palpated during cytoreductive surgery and only clinically suspicious (enlarged, firm, or fixed) lymph nodes are removed.

Patients with PPA presenting with clinically or surgically detectable lymphadenopathy confirmed by histologic examination to be secondary to involvement with PPA metastases were identified. The clinical and pathological characteristics of node-positive patients (group A) were recorded and compared with those of node-negative patients (group B). Performance status was assessed according to the Gynecologic Oncology Group (GOG) criteria. Response to chemotherapy was assessed according to the World Health Organization (WHO) criteria [22]. Patients were followed until death or 30 June 1997. Overall survival was calculated from the time of surgical diagnosis to the time of death or last follow-up. Survival of patients in group A was assessed and compared to that of patients in group B. Statistical analysis was performed using the Fisher exact and exact chi-square tests. Survival curves were constructed according to the method described by Kaplan and Meier [23]. Difference in survival was compared using the exact log-rank test [24] (StatXact, Cytel Software, Cambridge, MA). *P*-values were based on two-tailed tests and considered significant at $P < 0.05$.

RESULTS

Our search confirmed the diagnosis of PPA in 72 patients seen at RPCI between October 1982 and October 1996. Eight patients presented with lymph node enlargement confirmed to be secondary to PPA tumor deposits. The incidence of lymphadenopathy as one of the clinical/surgical presenting features in patients with PPA was 8/72 [11.1%, 95% confidence interval (CI): 5–21%]. The sites of lymph node enlargements were inguinal (n = 4), inguinal + pelvic (n = 1), inguinal + periarotic (n = 1), pelvic (n = 1), and periaortic (n = 1). Figure 1 demonstrates the histologic appearance of lymph node involvement in one of the study patients.

All patients underwent laparotomy and primary cytoreductive surgery. Surgical staging was performed retrospectively in patients who did not undergo initial surgical staging based on the available operative and pathological data. Sixty-eight patients received postoperative (mostly platinum-based multiagent) chemotherapy. Four patients did not receive postoperative chemotherapy: two patients died within 1 month of the initial surgical procedure, one patient had poor performance status and was judged not to be a candidate for chemotherapy, and one patient refused chemotherapy. No patient was lost to follow-up. The median duration of follow-up of patients who received chemotherapy (n = 68) was 16.8 months (range: 2.7–140.8 months). The estimated median overall survival of all patients (n = 72) was 21.2 months (SE = 2.7 months). The estimated median overall survival of patients who received chemotherapy (n = 68) was 23.5 months (95% CI: 18.9–39.8 months).

As demonstrated in Tables I and II there were no significant differences with regard to the clinicopathologic characteristics or first-line chemotherapy treatment of the patients in group A and group B. As shown in Table III, the overall response to chemotherapy in group A was not significantly different from that in group B (71.4% vs. 69.7%, respectively, $P = 1.0$).

At the time of last follow-up, 37 patients with negative lymph nodes and 3 patients with positive lymph nodes were dead of disease, 10 patients with negative lymph nodes and 3 patients with positive lymph nodes were alive with disease, 11 patients with negative lymph nodes and 2 patients with positive lymph nodes were alive with no evidence of disease, and 2 patients with negative lymph nodes were dead from causes other than cancer.

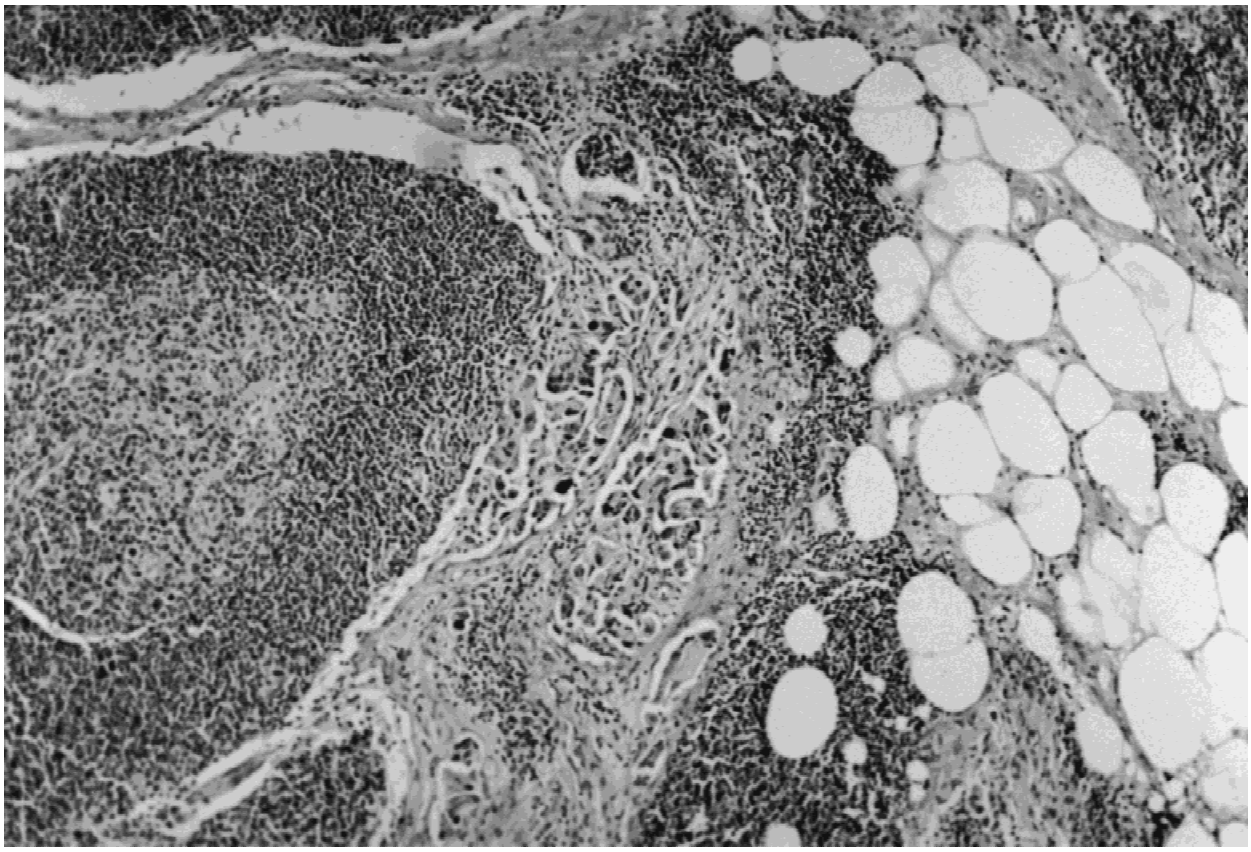

Fig. 1. Paraaortic lymph node with sinusoidal infiltrate of metastatic serous carcinoma (hematoxylin-eosin, ×100).

The estimated median overall survival of group A patients was 21.5+ months (range: 6.0–104.4 months). The estimated median overall survival of group B patients was 23.5 months (range: 2.7–140.8 months). As demonstrated in Figure 2, there was no statistically significant difference ($P = 0.14$) in survival among women with or without lymph node involvement.

DISCUSSION

The current study demonstrates that lymphadenopathy was a presenting feature in approximately 11% (8/72) of patients with PPA. Since pelvic and periaortic lymphadenectomy was not performed in all of our patients, it is possible that the incidence of microscopic involvement of lymph nodes in patients with PPA is higher than the 11% figure reported in the current study.

Several reports [7,15–17,25,26] comparing patients with PPA to those with ovarian carcinoma or primary peritoneal mesothelioma have not commented on the incidence and/or significance of lymph node involvement.

Fromm et al. [14] reported on 74 patients with PPA. They described involvement of periaortic lymph nodes in 7/24 patients (29.2%) and involvement of pelvic lymph nodes in 3/15 patients (20.0%). These authors [14] reported one patient who presented with inguinal lymphadenopathy and another patient who presented with axillary lymphadenopathy, but did not evaluate survival among patients with pathologically demonstrable nodal metastases as a separate subgroup. Dalrymple et al. [12] described inguinal lymph node involvement in 3/31 patients with PPA. Absent the brief mention of lymph node involvement in these reports [12,14], we could not find any references on the incidence of lymph node involvement in patients with PPA. Additionally, no reference of the prognostic significance of lymph node involvement among patients with PPA is available for comparison to the current study.

In the current study, patients with PPA and positive lymph nodes did not differ significantly from patients with PPA and negative lymph nodes in terms of their clinicopathologic features, first-line chemotherapy treatment, method of assessment of response to therapy, response to chemotherapy, or overall survival.

Lymphatic drainage of the peritoneal cavity in women has not been fully studied. A lymphangiographic study following intraperitoneal injection of Thorotrast® in rats [27] demonstrated that the lymphatics of the diaphragm were filled first, draining both cranially and caudally. The most important pathways from the peritoneal cavity were the parasternal lymphatics with a small amount of

TABLE I. Comparison of the Clinicopathologic Features of Patients With PPA and Positive (Group A) vs. Negative (Group B) Lymph Nodes

	Number (%)		
Clinicopathologic features	Group A (n = 8)	Group B (n = 60)	*P**
Age (years)			
Median (SE)	61.5 (2.3)	65.0 (2.0)	0.40
Range	56–69	26–82	
Stage[a]			1.0
IIC	0 (0.0)	1 (1.7)	
IIIB	1 (12.5)	3 (5.0)	
IIIC	6 (75.0)	46 (76.7)	
IV	1 (12.5)	10 (16.7)	
Grade			1.0
1	0 (0.0)	4 (6.7)	
2	2 (25.0)	17 (28.3)	
3	6 (75.0)	39 (65.0)	
Ovaries			0.53
Absent	2 (25.0)	8 (13.3)	
No involvement	2 (25.0)	6 (10.0)	
Serosal involvement	2 (25.0)	25 (41.6)	
Superficial cortical involvement	2 (25.0)	21 (35.0)	
Surgical debulking			1.0
Optimal[b]	6 (75.0)	40 (66.7)	
Suboptimal	2 (25.0)	20 (33.3)	
Performance status[c]			0.58
Median	1	1	
Range	0–2	0–2	

[a]According to the FIGO staging system for ovarian carcinoma.
[b]Less than 1.0 cm largest residual tumor mass.
[c]According to the GOG criteria.
**P*-values were calculated according to the Fisher exact or exact chi-square method except for age, where it was calculated according to the Mann-Whitney test, and all were non-significant.

TABLE II. Comparison Between First-Line Chemotherapy in Patients With PPA and Positive (Group A) vs. Negative (Group B) Lymph Nodes

	Number (%)		
Chemotherapy type	Group A (n = 8)	Group B (n = 60)	*P**
Platinum-based multiagent	6 (75.0)	33 (55.0)	0.50
Platinum-paclitaxel	2 (25.0)	22 (36.7)	
Others[a]	0 (0.0)	5 (8.4)	

[a]Includes four patients who received single-agent cisplatin and one patient who received melphalan.
**P*-value was not statistically significant.

TABLE III. Comparison of Response to First-Line Chemotherapy in Patients With PPA and Positive (Group A) vs. Negative (Group B) Lymph Nodes

	Number (%)		
	Group A (n = 8)	Group B (n = 60)	*P**
Assessment of response			1.0
Clinical	3 (37.5)	22 (36.7)	
Surgical	4 (50.0)	34 (56.7)	
Laparotomy	3 (75.0)	26 (76.5)	
Laparoscopy	1 (25.0)	8 (23.5)	
Non-evaluable	1 (12.5)	4 (6.7)	
Type of response			1.0
Overall response	5 (71.4)	39 (69.7)	
Complete response	4 (57.1)	9 (16.1)	
Partial response	1 (14.3)	30 (53.6)	
Progressive disease	2 (28.6)	9 (16.1)	
Stable disease	0 (0.0)	8 (14.2)	

**P*-values were statistically non-significant.

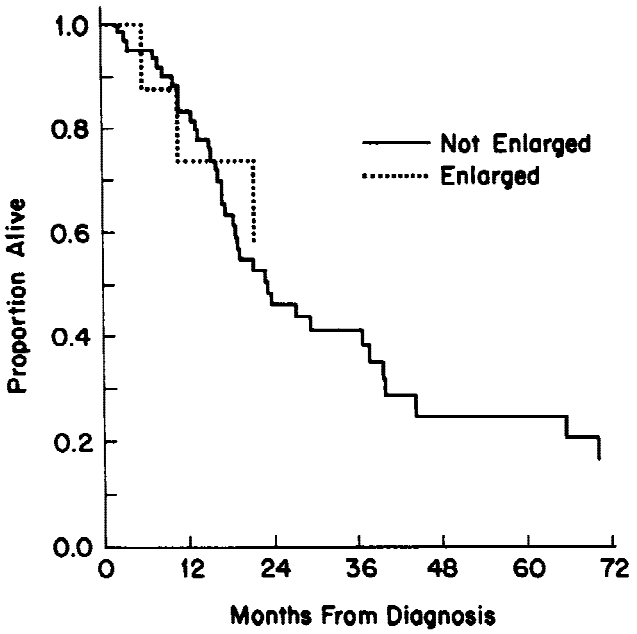

Fig. 2. Overall estimated survival curves of node-positive (n = 8) vs. node-negative (n = 60) patients with PPA ($P = 0.14$).

Thorotrast® found in the thoracic duct [27]. We think that the spread of PPA to the inguinal lymph nodes, the most commonly involved group of lymph nodes in our patients, might be explained by lymphatic spread along the round ligaments. Involvement of pelvic and periaortic lymph nodes might be explained by retrograde spread from the lymphatics of the diaphragm or through involvement of the ovaries or other pelvic or abdominal organs with PPA.

Despite several reports [19–21] which have described a high incidence of pelvic and/or periaortic lymph node involvement in patients with advanced stage epithelial ovarian cancer and the belief that surgical cytoreduction is the cornerstone of ovarian cancer treatment, the benefit of systematic pelvic and periaortic lymphadenectomy in these patients remains controversial. Oncologists who recommend routine lymphadenectomy cite reports which describe a therapeutic benefit to systematic pelvic and periaortic lymphadenectomy [21], as well as the obser-

vation of some investigators that lymph nodes act as a pharmacologic sanctuary in patients with epithelial ovarian cancer [28]. Opponents of systematic node dissection have opined that there is no consensus on the therapeutic value of systematic lymphadenectomy [29] and that the procedure may increase the risk for morbidity and prolong operating time [30].

CONCLUSIONS

Lymph node involvement is not an infrequent occurrence in women with PPA. Lymph node involvement does not seem to adversely affect survival in this group of patients. However, the significance of this lymph node spread and of routine lymphadenectomy in patients with PPA awaits further studies.

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